Facile synthesis of heterocycles having bacteriocidal activity incorporating oleic acid residues

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Synthesis of various heterocycles having fatty acid residues is described using ethyl-4-(hexadec-7-enyl)-3-oxobutanoate as starting material by reaction with different reagents. Preliminary antibacterial testing showed that the compounds ethyl-4-(hexadec-7-enyl)-3-oxobutanoate and 3-[octadec-9-ene-1-one]-chromen-2-one are the most promising.

Key words: Meldrum's acid, oleic acid, fatty acids, oximes, heterocycles

A search in the literature showed that heterocycles containing oleoyl residues possess bacteriocidal activity.[1,2] Oil wastes obtained from refinery factories are a big problem in Egypt and in an attempt to make use of these wastes, we try in this investigation to use oleic acid separated from the waste as a starting material to prepare some new heterocycles with anticipated bacteriocidal activity.[3-5]

With this aim oleoyl chloride **1** was used to acylate Meldrum's acid) in the presence of pyridine. The resulting acylated Meldrum's acid **3** was subjected to an acidic aqueous work up, and immediately thereafter refluxed in absolute ethanol[6] to give the β-keto ester **4** in good yield (*cf.* Scheme 1). The ^{1}H NMR spectrum of ethyl-4-(hexadec-7-enyl)-3-oxobutanoate **4** revealed the active methylene group at δ = 3.35 ppm, and moreover the ^{13}C NMR showed signals at 202.36 and 166.87 ppm, attributed to the two carbonyl groups.

Compound **4** was reacted with N,N-dimethyl formamide dimethylacetal as a one-carbon synthon to yield the 3-dimethylamino propenoate derivative **5**. In the ^{1}H NMR spectrum there appears a new broad signal at δ = 2.96 ppm characteristic of the dimethylamino group along with the methine-H at 7.59 ppm. Additionally, the mass spectrum of **5** reveals a molecular ion peak at *m/z* = 408 corresponding to the molecular formula $C_{25}H_{45}NO_3$.

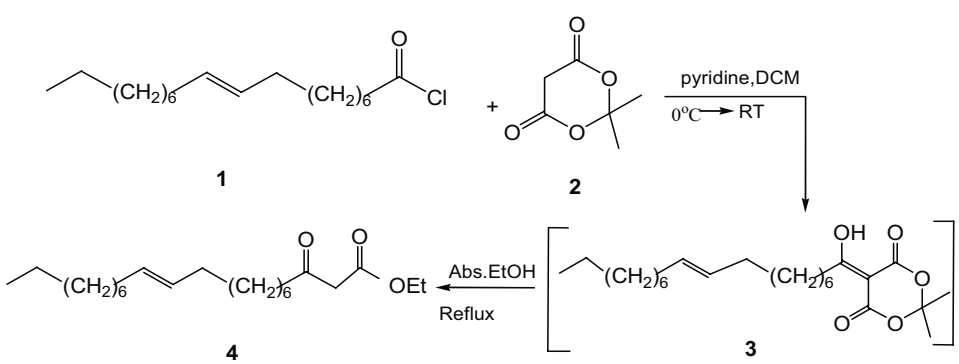
Enamine **5,** reacts with phenylhydrazine in acetic acid giving pyrazole-3-one derivative **6**. The mass spectrum of **6** gave a molecular ion peak at *m/z* = 424 which was in accordance with the proposed molecular weight.

Continuing our investigation, the β-keto ester **4** was allowed to react with thiourea in the presence of sodium ethoxide to give the uracil derivative **7** having the fatty residue at position 6 (*cf.* Scheme 2). The ^{1}H NMR of **7** showed a new exchangeable broad signal at δ = 12.34 characteristic for the uracil NH protons,[7] in addition to the uracil H-5 at 5.70 ppm, while its MS is in accord with the molecular formula $C_{21}H_{37}N_2OS$ (*m/z* = 366).

The β-keto ester **4** was also treated with salicylaldehyde in refluxing acetic acid to yield the expected coumarin derivative **8**. The ^{1}H NMR of **8** showed the characteristic coumarinyl H-4 at δ = 8.75 ppm.[8] Moreover, the ^{13}C NMR revealed signals at 197.40 and 158.22 ppm corresponding to the two carbonyl groups.

Moreover, compound **4** was treated with hydrazine hydrate in acetic acid/ethanol mixture to yield the pyrazole-5-one **9**. Pyrazolone **9** exists in the enol form and further the IR spectrum does not show the peak characteristic for the pyrazolone carbonyl group. When the pyrazolone **9** reacted with sodium nitrite in the presence of acetic acid, 4-hydoxyimino derivative **10a** was obtained in good yield. Its ^{1}H NMR showed the hydroxyl proton as a D_2O exchangeable signal at δ = 11.40 ppm; instead of the pyrazolone CH_2 protons signal previously detected in the parent **9**, while the mass spectrum of **10a** showed a molecular ion peak at 350 which was in a good agreement with its molecular formula $C_{20}H_{35}N_3O_2$.

Diazotisation of the pyrazole **9** in ethanol in the presence of sodium acetate, yielded the pyrazolone-4-azo phenyl derivative **10b** in a moderate yield. The ^{1}H NMR of compound **10b** showed the phenyl azo protons at δ = 7.26–7.60 ppm. Moreover, reaction of the pyrazolone derivative **9** with benzylidine malononitrile in the presence of sodium ethoxide, gave pyrazole derivative **11** with its characteristic pyran 4-H proton at δ = 4.61 ppm.[9] On the other hand, the β-keto ester **4** was treated with phenylhydrazine in the presence of acetic acid; a new N-phenylpyrazolone was obtained in satisfactory yield. All the elemental and spectral data were in accord with the suggested structure of the pyrazolone derivative **12**. Acetylation of **12** with acetyl chloride in the presence of calcium hydroxide yielded the 4-acetyl pyrazolone derivative **13** in good yield (*cf.* Scheme 3). The ^{1}H NMR of compound **13** showed acetyl protons at



Scheme 1

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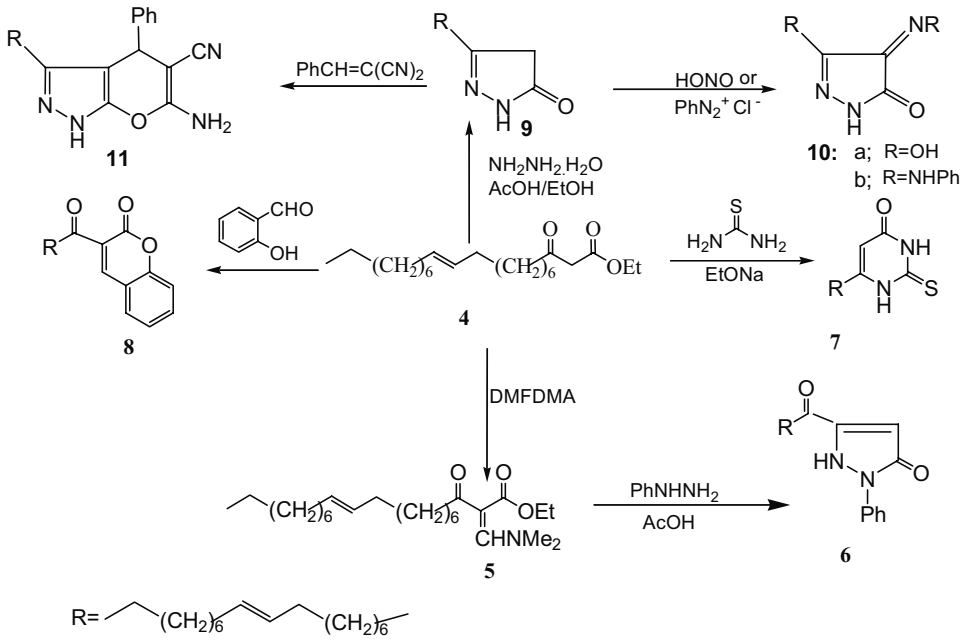
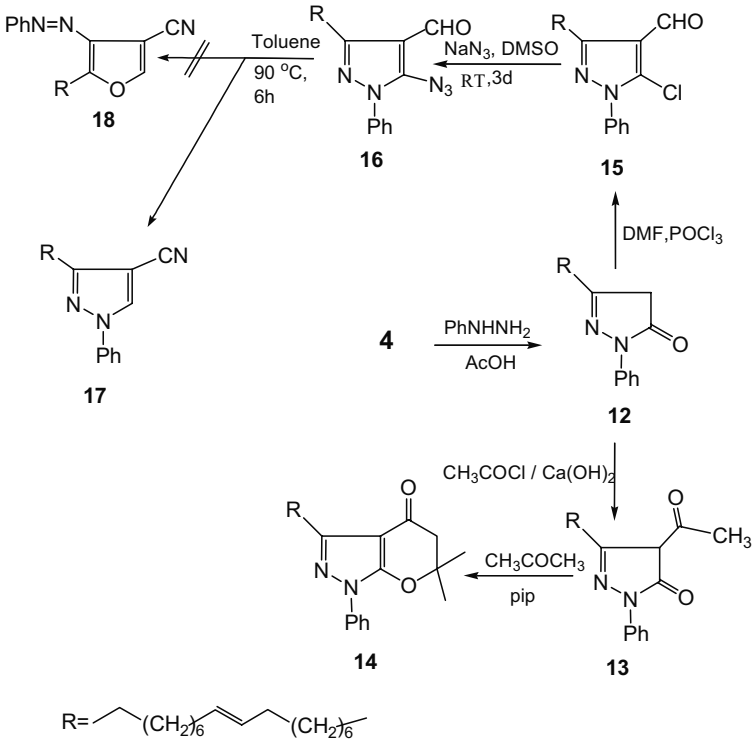


Scheme 2

2.21 ppm in addition to the other protons which are detected in the parent **12** (*cf*. Experimental).

Reaction of the 4-acetyl pyrazolone **13** with acetone in the presence of piperidine, gave the pyranopyrazole derivative **14** in good yield. The ^{1}H NMR showed a new active methylene group at δ = 2.70 ppm; characteristic for the chromanone CH_2-protons.[10,11] Moreover, the mass spectrum of compound **14** revealed a molecular ion peak at *m/z* = 479 which was in an accord with its molecular formula $C_{31}H_{46}N_2O_2$.

Sevenstrup *et al.*[12] demonstrated that highly substituted furans and pyrazoles can be formed from readily available starting materials in a few synthetic steps by thermolysis of 5-azido pyrazoles. Continuing our previous studies on the thermal rearrangement of 5-azido-4-formyl pyrazole derivatives,[6] the pyrazole derivative **12** was subjected to a Vilsmeier–Haack chloroformylation,[13] yielding the 5-chloro-4-formyl pyrazole derivative **15** in good yield (*cf*. Scheme 3). The ^{1}H NMR of **15** showed a new signal at δ = 9.94 ppm; characteristic for a CHO proton[6] with absence of the active methylene protons which were detected in the parent **12.** The mass spectrum of **15** showed a molecular ion peak at *m/z* = 443 which fitted the proposed molecular weight. In the next step, the 5-chloro-4-formyl pyrazole **15** was converted to the corresponding azide **16** by reaction with sodium azide.



Scheme 3

Finally, the azide **16** was subjected to thermolysis by heating in toluene at 90 °C for 6 h. The reaction afforded a sole product showing in the IR CN at ν = 2230 cm^{-1} and lacking the aldehydic carbonyl group which appears at ν = 1684 cm^{-1} in the parent **16**. Moreover the ^{1}H, ^{13}C NMR and mass spectra supported the structure **17** not structure **18** (*cf.* Experimental and Scheme 3).This result was in good agreement with our previous report.[6]

Reaction of **15** with benzil in refluxing acetic acid, afforded the 4-imidazolyl pyrazole derivative **19** in fairly good yield. The ^{1}H NMR showed an exchangeable NH proton at δ = 12.47 ppm; with the disappearance of the aldehydic proton present in the parent at δ = 9.94 ppm.[14] Additionally, **15** was treated with ethyl cyanoacetate in the presence of piperidine to yield the ylidene ethyl cyanoacetate derivative **20**, which was subjected to reaction with acetophenone in the presence of excess ammonium acetate to give the 3-dihydropyridine derivative **21** (*cf.* Scheme 4). All elemental and spectral data of compounds **20** and **21** were in agreement with the suggested structures (*cf.* Experimental)

The antimicrobial activity

The preliminary antibacterial test showed that compounds **4**, **7**, **8**, **10a**, **10b**, **11** possess activity against Gram positive bacteria G^{+} (*staphylococcus aureus*) and Gram negative bacteria G^{-} (*Escherichia coli*). However the most promising results were found with compounds **4** and **8** (*cf.* Table 1).

In compounds **4** and **8**, it seems that the presence of the fatty chain in the form of an acyl residue enhanced the bacteriocidal activity (*cf.* Table I). This could be attributed to the presence of the fatty residue in compounds **4** and **8** as oleic acid is known for its bacteriocidal activity.[1,2]

Conclusion

In summary, we report on the synthesis of various nitrogen heterocyclic compounds having oleolyl residues. Preliminary antibacterial testing of these heterocycles showed that compounds **4** and **8** were the most promising.

Table 1 The antimicrobial activity screening of the prepared compounds at concentration 2mg/disc compared with the reference drug Tetracycline

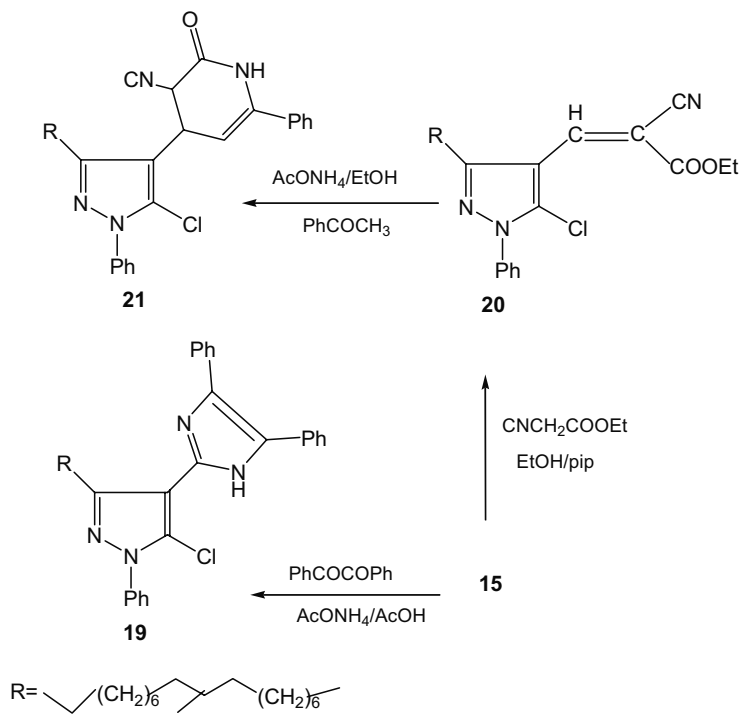
Compounds	Inhibition zone diameter (mm mg^{-1})	
	Escherichia coli(G^{-})	Staphylococcus *aureus*(G^{+})
Tetracycline	32	43
4	13	14
7	13	12
8	14	14
10a	10	10
10b	12	12
11	10	11

Where: Inhibition zone: High activity ≥ 12 (mm), Moderate activity 9–11 (mm), Slight activity 7–8 (mm) and Non sensitive 0–6 (mm).

Experimental

All melting points are uncorrected. IR, NMR and mass spectra were recorded on: IR spectra (KBr): Pye-Unicum SP-1100. ^{1}H NMR and ^{13}C NMR spectra: Jeol 500 MHZ, with internal standard tetramethylsilane (TMS). Mass spectra: Jeol JMS-AX500. Elemental analyses (in accord with the calculated values) were carried out in the Micro analytical Unit, Faculty of Science, Cairo University. Precoated silica gel 60 F_{254} plates with a layer thickness 0.25 nm from Merck were used for thin layer chromatography. Yields are not optimised.

Ethyl-4-(hexadec-7-enyl)-3-oxobutanoate **(4)**: To a solution of **2** (1.44 g, 10 mmol) in methylene chloride (10 mL) in a round-bottomed flask (250 mL), equipped with an additional funnel and nitrogen inlet and cooled to 0 °C, pyridine (2.5 mL) was added dropwise over 10 min., followed by the addition of a freshly prepared solution of oleoyl chloride (2.82 g, 10 mmol) which resulted in an orange solution. After complete addition (2 h), the resulting dark orange solution was stirred for an additional one hour. The solution was diluted with methylene chloride (10 mL) and poured into 2M HCl and ice. The two phases were separated and the aqueous phase was extracted with methylene chloride (2 × 50 mL).The combined organic phases were washed with 2M HCl (2 × 50 mL), dried over anhydrous sodium sulfate, and evaporated.The resulting organic oil was refluxed in anhydrous ethanol (50 mL) for 2.5 h, the solvent removed *in vacuo* leading to a dark oil which was purified by column chromatography (silica gel, ethyl acetate/pet.ether 1:9, R_f = 0.5) to give **4** as a pale yellow oil (2.29 g) in 65% yield. IR (KBr): ν_{max} 2926, 2854(CH), 1738



Scheme 2

(CO, ester), 1651 (CO), 1632 (C=C) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 0.91 (t, 3H, CH_3-), 1.14–1.62 (m, 25H, 11 × CH_2, CH_3-ester), 2.05(m, 4H, 2 × CH_2), 2.54(t, 2H, *J* = 7.08 Hz, CH_2), 3.35(s, 2H, CO CH_2 CO), 4.25 (q, 2H, *J* = 6.6 Hz, CH_2-ester), 5.35 (m, 2H, CH=CH) ppm. ^{13}C NMR (500 MHz, $CDCl_3$): 13.68, 13.83(CH_3-), 22.34, 23.04, 26.79, 26.83, 28.74, 28.80, 29.05, 29.15, 29.20, 29.33, 29.42, 31.48, 31.58, 42.52, 48.79, 60.77 (CH_2-), 129.51, 130.00 (C-9, C-10), 166.87(CO ester), 202.36(CO). M S: *m/z* (%) = 352 [M^+].Anal. Calcd for $C_{22}H_{40}O_3$ (352.56): C, 74.95; H, 11.44. Found: C, 74.80; H, 11.30%.

Ethyl-4-(hexadec-7-enyl)-2-[(dimethylamino)methylene]-3-oxobutanoate **(5)**: A mixture of **4** (3.52 g, 10 mmol) and N,N-dimethyl formamide dimethylacetal (1.19 g, 10 mmol) in benzene (20 mL) was refluxed at 70 °C for 2 h. The solvent was removed *in vacuo*, leading to an oil which was purified by column chromatography (silica gel, ethyl acetate/pet.ether 2:3, R_f = 0.4) to give **5** as a yellow oil (2.85 g) in 70% yield. IR (KBr): ν_{max} 2925, 2856 (CH), 1740 (CO, ester), 1693 (CO), 1634 (C=C) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 0.95 (t, 3H, CH_3-), 1.22–1.37 (m, 23H, 10 × CH_2, CH_3 ester), 1.56 (m, 2H, CH_2), 1.97 (m, 4H, 2 × CH_2), 2.60 (t, 2H, CH_2), 2.96 (brs, 6H, 2 × CH_3), 4.11 (q, 2H, CH_2- ester), 5.30 (m, 2H, CH=CH), 7.59 (s, 1H, =CH) ppm. MS: *m/z* (%) = 408 [M^+].Anal. Calcd for $C_{25}H_{45}NO_3$ (407.63): C, 73.66; H, 11.13; N, 3.44. Found: C, 73.50; H, 11.30; N, 3.40%.

4-[Octadec-9-ene-2-one]-2H-1-phenylpyrazolo-5-one **(6)**: A solution of **5** (4.07 g, 10 mmol) and phenylhydrazine (1.08 g, 10 mmol) in acetic acid (20 mL) was refluxed for 2 h. The solution was poured onto water (100 mL) and the organic phase extracted with ethyl acetate and dried over anhydrous sodium sulfate. Removal of the solvent *in vacuo* left an oily residue, which was solidified by drops of ethyl alcohol, collected, dried and recrystallised to give **6** as white crystals m.p. = 130–133 °C (2.75 g) in 65% yield (ethanol). IR (KBr): ν_{max}3222 (NH), 1680, 1665 (2 CO), 1606 (C=C) cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6):δ 0.85 (t, 3H, CH_3-), 1.15–1.42 (m, 22H, 11x CH_2-), 1.61–1.80 (m, 2H, CH_2-), 1.89–2.04 (m, 4H, 2 × CH_2-), 5.34 (m, 2H, CH=CH), 7.24–7.62 (m, 5H, ArH), 11.59 (s, 1H, NH) ppm. M S: *m/z* (%) = 424[M^+]. Anal. Calcd for $C_{27}H_{40}N_2O_2$ (424.63): C, 76.37; H, 9.50; N, 6.60. Found: C, 76.20; H, 9.60; N, 6.70%.

6-Heptadec-8-enyl-2-thiouracil **(7)**: A mixture of **4** (3.52 g, 10 mmol), thiourea (0.76 g, 10 mmol) and sodium (0.23 g) in absolute ethanol (20 mL) was refluxed for 3 h.The reaction mixture was cooled, poured over crushed ice and finally acidified with HCl. The precipitate which was formed was collected and recrystallised to give **7** as a white powder m.p. = 131–132 °C (2.55 g) in 70% yield (ethanol). IR (KBr): ν_{max} 3105(NH), 2920, 2852(CH), 1661 (CO), 1580 (C=C) cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 0.85 (t, 3H, CH_3-), 1.15–1.35 (m, 22H, 11 × CH_2-), 1.42–1.59(m, 2H, CH_2-), 1.89–2.04 (m, 4H, 2 × CH_2-), 5.32 (m, 2H, CH=CH), 5.70(s, 1H, uracil H-5), 12.34 (brs., 2H, 2NH) ppm. M S: *m/z* (%) = 366 [M^+] Anal. Calcd for $C_{21}H_{37}N_2OS$ (365.60): C, 68.99; H, 10.20; N, 7.66. Found: C, 68.90; H, 10.30; N, 7.70%.

3-[Octadec-9-ene-1-one]-chromen-2-one **(8)**: To a mixture of **4** (3.52 g, 10 mmol) and salicylaldehyde (1.22 g, 10 mmol) in absolute ethanol (20 mL) triethylamine (three drops) was added and refluxed for 9 h. A precipitate was formed after cooling, filtered off, washed with ethyl alcohol (10 mL), dried and recrystallised to give **8** as white crystals m.p. 63–65 °C (3.48 g) in 85% yield. IR (KBr): ν_{max} 2920, 2852 (CH), 1734 (CO, chromanone), 1681 (CO), 1608 (C=C) cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6):δ 0.91 (t, 3H, CH_3-), 1.21–1.62 (m, 24H, 12 × CH_2-), 2.01 (m, 4H, 2 × CH_2-), 5.32 (m, 2H, CH=CH), 7.33–7.49 (m, 2H, ArH),7.62–7.75 (m, 1H, ArH),7.81–7.95 (m, 1H, ArH), 8.75 (s, 1H, coumarinyl H-4) ppm. ^{13}C NMR (500 MHz, $CDCl_3$): δ 13.25 (CH_3-), 21.80, 22.98, 26.32, 28.75, 28.83, 28.89, 29.00, 29.07, 29.11, 29.14, 29.19, 31.02, 41.69 (CH_2-), 115.77, 117.43, 124.06, 128.88, 128.93, 154.30, (C-aromatic), 129.47, 129.59 (C-9, C-10), 133.35, 146.48 (C-3, C-4 chromene), 158.22 (CO), 197.40 (chromene CO). M S: *m/z* (%) = 411[M^+].Anal. Calcd for $C_{27}H_{38}O_3$ (410.59): C, 78.98; H, 9.33. Found: C, 79.10; H, 9.40%.

3-(Heptadec-8-enyl)-1H-pyrazol-5-one **(9)**: To the stirred cooled solution of compound **4** (3.52 g,10 mmol) in acetic acid/ethanol (3 : 1) hydrazine hydrate (0.5 mL, 10 mmol) was added dropwise within 15 min. After the addition was completed, the reaction mixture was stirred at room temperature for another 2 h., the solution was poured onto water (100 mL), the semi solid was formed and extracted with ethyl acetate (2 × 50 mL) and the solvent was removed *in vacuo* to give a semi-solid which was solidified using petroleum ether, collected and recrystallised to give **9** as a white solid m.p. = 160–162 °C (2.08 g) in 65% yield (ethanol). IR (KBr): ν_{max} 2924, 2853 (CH), 1613 (C=N) cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 0.85 (t, 3H, CH_3), 1.14–1.35 (m, 22H, 11 × CH_2), 1.41–1.60(m, 2H, CH_2), 1.97 (m, 2H, CH_2-), 2.36–2.42(m, 2H, CH_2-), 5.35 (m, 2H, CH=CH), 11.22 (brs., 1H, OH) ppm. MS: *m/z*(%) = 321[M^+].Anal. Calcd for $C_{20}H_{36}N_2O$ (320.51): C, 74.95; H, 11.32; N, 8.74; Found: C, 74.90; H, 11.50; N, 8.70%.

3-Heptadec-8-enyl4-hydroxyimino-1H-pyrazol-5-one **(10a)**: To a solution of **9** (3.2 g, 10 mmol) in acetic acid (20 mL), aqueous sodium nitrite (1.38 g, 20 mmol) was added portionwise, with stirring at 0–5 °C over a period of 20 min. A solid formed after 1 h, was filtered off, washed with water (50 mL) and recrystallised to give **10a** as a pale yellow powder, m.p. = 133–135 °C (2.44) in 70% yield (ethanol). IR (KBr): ν_{max} 3176 (NH), 2923, 2853 (CH), 1724 (CO), 1585 (C=C) cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 0.89 (t, 3H, CH_3-), 1.11–1.34 (m, 22H, 11 × CH_2-), 1.40–1.62 (m, 2H, CH_2), 1.87–2.01 (m, 4H, 2 × CH_2-), 5.35 (m, 2H, CH=CH), 11.40 (s, 1H, -OH), 13.74 (brs., 1H, NH) ppm. M S: *m/z* (%) = 350 [M^+].Anal. Calcd for $C_{20}H_{35}N_3O_2$ (349.51): C, 68.73; H, 10.09; N, 12.02. Found: C, 68.80; H, 10.20; N, 12.10%.

3-Heptadec-8-enyl-4-phenylazo-1H-pyrazol-5-one **(10b)**: To the stirred cooled solution of **9** (3.2 g, 10 mmol) and sodium acetate (5.1 g, 80 mmol) in dioxane (20 mL), the diazonium salt of aniline was added and the temperature was kept at (0–5 °C) for about 1 h. After removing the ice bath, the stirring was maintained for 30 min. and water added (100 mL). The precipitate was filtered off, collected, washed many times with water and recrystallised to afford **10b** as yellow crystals m.p. = 101–103 °C (3.18 g) in 75% yield (ethanol). IR (KBr): ν_{max} 3176(NH), 2919, 2850(CH), 1666 (CO), 1602 (C=C) cm^{-1}. ^1H NMR (500 MHz, DMSO- d_6): δ 0.84 (t, 3H, CH_3-), 1.15–1.41(m, 22H, 11 × CH_2), 1.65 (m, 2H, CH_2 -), 1.95 (m, 4H, 2 × CH_2-), 5.35 (m, 2H, CH=CH), 7.15 (brs., 1H, NH-Ar), 7.26–7.60 (m, 5H, ArH), 11.61 (s, 1H, NH) ppm. M S: *m/z* (%) = 424[M^+].Anal. Calcd for $C_{26}H_{40}N_4O$ (424.62): C, 73.54; H, 9.49; N, 13.19. Found: C, 73.40; H, 9.60; N, 13.20%.

3-(Heptadec-8-enyl)-5-Cyano-4-phenyl-1,4-dihydropyrano[2,3-c] pyrazol-6-ylamine **(11)**: A solution of **9** (3.2 g, 10 mmol) and benzylidene malononitrile (1.45 g, 10 mmol) was refluxed in absolute ethanol (30 mL) in the presence of triethylamine (5 drops) for about 12 h. When the reaction mixture cooled the solid was collected and recrystallised to afford **11** as white crystals m.p. = 186–188 °C (3.79 g) in 80% yield (ethanol). IR (KBr): ν_{max} 3465, 3228 (NH_2), 3119 (NH), 2924, 2853 (CH), 2197 (CN), 1635 (C=N), 1602 (C=C) cm^{-1}. ^1H NMR (500 MHz, DMSO- d_6): δ 0.89(t, 3H, CH_3-), 1.09–1.42 (m, 26H, 13 × CH_2), 1.92–2.05 (m, 2H, CH_2), 4.61 (s, 1H, CH-), 5.35 (m, 2H, CH=CH), 6.85 (s, 2H, NH_2), 7.15–7.40 (m, 5H, ArH), 12.15 (s, 1H, NH) ppm. M S: *m/z* (%) = 474 [M^+]. Anal. Calcd for $C_{30}H_{42}N_4O$ (474.31): C, 75.91; H, 8.92; N, 11.80. Found: C, 76.00; H, 8.80; N, 11.60%.

3-Heptadec-8-enyl-1-phenyl-1, 5-dihydropyrazol-5-one **(12)**: To the stirred solution of compound **4** (3.52 g, 10 mmol) in acetic acid/absolute ethanol 3:1 phenylhydrazine (1.08 mL, 10 mmol) was added dropwise within 15 min. After the addition was completed, the reaction mixture was stirred at room temperature for 2 h. and then the solution was poured into cold water, the organic phase extracted with ethyl acetate and dried over anhydrous sodium sulfate. Removal of the solvent left an oily residue which was purified by column chromatography (silica gel, ethyl acetate/pet. ether 1:4, R_f = 0.3) to give **12** as a yellow oil (2.77 g) in 70% yield. IR (KBr): ν_{max} 2925, 2855(CH), 1717(CO), 1601(C=N) cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6):δ 0.79 (t, 3H, CH_3-), 1.08–1.35 (m, 24H, 12 × CH_2-), 1.40–1.61 (m, 2H, CH_2-), 1.91–2.09 (m, 4H, 2 × CH_2-), 5.29 (m, 2H, CH=CH), 7.01–7.71 (m, 5H, ArH) ppm. MS: *m/z* (%) = 397[M^+].Anal. Calcd for $C_{26}H_{40}N_2O$ (396.61): C, 78.74; H, 10.17; N, 7.06. Found: C, 78.60; H, 10.30; N, 7.10%.

4-Acetyl-3-heptadec-8-enyl-1-phenyl-1, 5-dihydropyrazol-5-one **(13)**: To a stirred solution of **12** (3.96 g, 10 mmol) and acetyl chloride (0.78 g, 10 mmol) in dioxane (50 mL) at room temperature, $Ca(OH)_2$ powder was added portionwise. After 1 h the reaction mixture was filtered to remove $Ca(OH)_2$ and the filtrate was evaporated *in vacuo* to give an oily residue purified by column chromatography (silica gel, ethyl acetate/pet. ether 0.3: 5 R_f = 0.51) to afford **13** as a brown oil (3.5 g) in 80% yield IR (KBr): ν_{max} 2925, 2855 (CH), 1790 (CO), 1722 (CO), 1597 (C=C) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 0.85 (t, 3H, CH_3-), 1.10–1.42 (m, 20H, 10 × CH_2-), 1.59–1.79 (m, 2H, CH_2-), 2.10 (m, 4H, 2 × CH_2), 2.21 (s, 3H, $COCH_3$), 2.63(m, 2H, CH_2), 5.32 (m, 2H, CH=CH), 6.10 (s, 1H, CH-), 7.21–7.59 (m, 5H, ArH) ppm. M S: *m/z* (%) = 439[M^+].Anal. Calcd for $C_{28}H_{42}N_2O_2$ (438.62): C, 76.67; H, 9.65; N, 6.39. Found: C, 76.50; H, 9.80; N, 6.40%.

3-(Heptadec-8-enyl)-6, 6 -dimethyl-5, 6-dihdro-1H-pyrano [2, 3-c] pyrazole-4-one **(14)**: A mixture of **13** (4.37 g, 10 mmol) and acetone

(0.58 mL, 10 mmol), in dry benzene (20 mL) in the presence of piperidine (seven drops) was refluxed for about 1 h using a Dean-Stark apparatus. The reaction mixture was poured into water and acidified by HCl. The organic layer was extracted with ethyl acetate, dried by anhydrous sodium sulfate and the solvent removed *in vacuo*. The oily residue was purified by column chromatography (silica gel, ethyl acetate/pet. ether 0.3:5, R_f = 0.45) to afford **14** as a pale yellow oil (3.2 g) in 67% yield. IR (KBr): ν_{max} 2924, 2854 (CH), 1693 (CO), 1627 (C=N), 1597 (C=C) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 0.87 (t, 3H, CH_3-), 1.27–2.49 (m, 34H, 14 × CH_2-, 2 × CH_3), 2.70(s, 2H, CH_2-), 5.37 (m, 2H, CH=CH), 7.17–7.97 (m, 5H, ArH) ppm. MS: *m/z* (%) = 479[M^+].Anal. Calcd for $C_{31}H_{46}N_2O_2$ (478.71): C, 77.78; H, 9.69; N,5.85. Found: C, 77.90; H, 9.60; N, 5.90%.

5-Chloro-3-heptadec-8-enyl-1-phenyl-1H-pyrazol-4-carbaldhyde **(15)**: To dry DMF (0.73 g, 10 mmol) cooled to 0 °C, $POCl_3$ (2 mL, 13 mmol) was slowly added at such a rate that the temperature was maintained below 10ºC followed by the addition of compound **12** (3.96 g, 10 mmol) in small portions. The resulting solution was stirred at room temperature for 30 min and at 50 °C for 1 h. The dark reaction mixture was then cooled to room temperature and poured slowly into ice/water and neutralised to pH 6.7 by adding Na_2CO_3 in small portions. The resulting brown oil was extracted with ethyl acetate (3 × 50 mL). The organic phase was washed with water (100 mL) and dried by anhydrous sodium sulfate. After removal of the solvent *in vacuo,* the oily residue was purified by column chromatography (silica gel, ethyl acetate/pet. ether, 1:9, R_f = 0.4) to give **15** as a pale brown oil (3.32 g) in 75% yield. IR (KBr): ν_{max} 2925, 2855 (CH), 1684 (CHO), 1596 (C=C) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 0.85 (t, 3H, CH_3-), 1.22–1.51 (m, 20H, 10 × CH_2-), 1.68 (m, 2H, CH_2-), 1.96 (m, 4H, 2 × CH_2), 2.88(m, 2H, CH_2-), 5.30 (m, 2H, CH=CH), 7.45–7.5 (m, 5H, ArH), 9.94 (s, 1H, CHO) ppm. M S: *m/z* (%) = 443[M^+]. Anal. Calcd for $C_{27}H_{39}ClN_2O$ (443.06): C, 73.19; H, 8.87; N, 6.32. Found: C, 73.30; H, 8.70; N, 6.50%.

5-Azido-3-heptadec-8-enyl-1-phenyl-1H-pyrazol-4-carbaldhyde **(16)**: To a solution of **15** (4.41 g, 10 mmol) in DMSO (25 mL) sodium azide (0.65 g, 10 mmol) was added and the reaction mixture stirred for 72 h at 35 °C in the absence of light. The solution was diluted with water (100 mL) and extracted with diethyl ether (3 × 50 mL). The organic phase was separated, washed with water (100 mL) and dried by anhydrous sodium sulfate. After removal of the solvent *in vacuo*, the oily residue was purified by column chromatography (silica gel, ethylacetate/pet. ether, 0.3: 5, R_f = 0.5) to give **16** as a yellow oil (3.14 g) in 70% yield. IR (KBr): ν_{max} 2925, 2854(CH), 1686 (C=O), 1631 (C=N), 1597 (C=C) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 0.87 (t, 3H, CH_3), 1.27–1.40 (m, 22H, 11 × CH_2), 1.63–1.73 (m, 2H, CH_2), 2.02–2.21 (m, 4H, 2 × CH_2), 5.36 (m, 2H, CH=CH), 7.51–7.56 (m, 5H, ArH), 9.99(s, 1H, CHO) ppm. MS: *m/z*(%) = 449[M^+]. Anal. Calcd for $C_{27}H_{39}N_5O$ (449.63): C, 72.12; H, 8.74; N,15.58. Found: C, 72.00; H, 8.80; N, 15.60%.

3-Heptadec-8-enyl-1-phenyl-1H-pyrazol-4-carbonitrile **(17)**: Compound **16** (4.46 g, 10 mmol) was dissolved in toluene (50 mL) in an atmosphere of dry N_2 and stirred at 100 °C. After 9 h, the reaction mixture was cooled to room temperature and the toluene was removed *in vacuo*. The resulting oil was purified by column chromatography (silica gel, ethyl acetate/pet. ether, 0.3: 5, R_f = 0.42) to afford **17** as a pale yellow oil (2.17 g) in 67% yield. IR (KBr): ν_{max} 2925, 2855 (CH), 2230 (CN), 1631 (C=N), 1597 (C=C) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 0.89(t, 3H, CH_3-), 1.27–2.31(m, 20H, 10 × CH_2-), 5.38 (m, 2H, CH=CH), 7.39–7.69 (m, 5H, ArH), 8.24 (s, 1H, CH=) ppm. ^{13}C NMR (500 MHz, $CDCl_3$): δ 14.05 (CH_3-), 22.63, 26.92, 27.07, 28.59, 28.68, 29.10, 29.23, 29.28, 29.54, 29.62, 29.66, 29.71, 31.85, 33.18(CH_2-), 118.83(CN), 119.55, 127.91, 129.53, 129.70, 129.74, 129.91, 130.17, 130.04, 132.58, 138.26 ppm. M S: *m/z* (%) = 406 [M^+]. Anal. Calcd for $C_{27}H_{39}N_3$ (405.62): C, 79.95; H, 9.69; N, 10.36. Found: C, 80.10; H, 9.50; N, 10.40%.

5-Chloro-3-heptadec-8-enyl-4-[2'-benzimidazolyl-4,5-diphenyl-1-phenyl-1H-pyrazole **(19)**: A mixture of **15** (4.41 g, 10 mmol), benzil (1.33 g, 10 mmol) and ammonium acetate (1.54 g, 20 mmol) in glacial acetic acid (50 mL) was heated under reflux until TLC showed complete conversion (*ca* 3 h). The reaction mixture was poured into water (100 mL), extracted with ethyl acetate and the combined ethyl acetate extracts were dried by anhydrous sodium sulfate. After removal of the solvent *in vacuo*, the crude product was purified by column chromatography (silica gel, ethyl acetate/pet. ether 1 : 4, R_f = 0. 4) to give **19** as a white solid m.p. 123–125 °C (5.19 g) in 82% yield. IR(KBr): ν_{max} 3138 (NH), 2923, 2852 (CH_2), 1599(C=C) cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 0.82(t, 3H, CH_3-), 1.21–1.62 (m, 20H, 10 × CH_2), 1.64 (m, 2H, CH_2), 5.27 (m, 2H, CH=CH), 7.30–7.61 (m, 15H, 3 × Ph), 12.47 (brs, 1H, NH) ppm. MS: *m/z* (%) = 634[M^+]. Anal. Calcd for $C_{41}H_{49}ClN_4$ (633.32): C, 77.76; H, 7.80; N, 8.85. Found: C, 77.60; H, 7.90; N, 8.90%.

4-[(1-Cyano-1-ethoxycarbonyl)ethyleno]-5-chloro-3-heptadec-8-enyl-1H-1-phenylpyrazole **(20)**: A mixture of **15** (4.41 g, 10 mmol) and ethyl cyanoacetate (1.29 g, 10 mmol) in absolute ethanol (50 mL) in the presence of piperidine (5 drops) was heated under reflux until TLC showed complete conversion (*ca* 2 h). The reaction mixture was poured into water (100 mL), acidified with concentrated HCl and extracted with ethyl acetate. The combined ethyl acetate extracts were dried by anhydrous sodium sulfate. After removal of the solvent *in vacuo*, the crude product was purified by column chromatography (silica gel, ethyl acetate/pet. ether 0.3:5, R_f = 0.27), to give **20** as a pale brown oil (4.19 g) in 78% yield. IR (KBr): ν_{max} 2926, 2858 (CH_2), 2224 (CN),1728 (COOEt.), 1607 C=C) cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 0.81(t, 3H, CH_3-), 1.20–1.62 (m, 23H, 10 × CH_2,CH_3-ester), 1.95 (m, 4H, 2 × CH_2), 2.79 (m, 2H, CH_2), 4.30 (q, 2H, *J* = 7.42 Hz, CH_2-ester), 5.28 (m, 2H, CH=CH), 7.30–7.58 (m, 5H, ArH), 8.18 (s, 1H, = CH) ppm. M S: *m/z* (%) = 539[M^+]. Anal. Calcd for $C_{32}H_{44}ClN_3O_2$ [538.16]: C, 71.42; H, 8.24; N, 7.81. Found: C, 71.20; H, 8.40; N, 7.80%.

3-Cyano-6-phenyl-4[4'(5'-chloro-3'-heptadec-8-enyl-1'-phenyl-1H-pyrazolyl)]1H-pyridin-2-one **(21)**: A mixture of **20** (5.37 g, 10 mmol), acetophenone (1.2 g, 10 mmol) and ammonium acetate (1.54 g, 20 mmol) in absolute ethanol (50 mL) was heated under reflux until TLC showed complete conversion (*ca* 4 h). The reaction mixture was poured into water (100 mL), extracted with ethyl acetate the combined ethyl acetate extracts were dried by anhydrous sodium sulfate. After removal of the solvent *in vacuo* the crude product was purified by column chromatography (silica gel, ethyl acetate/pet. ether 1:4, R_f = 0.27) to give **21** as a colourless oil (3.72 g) in 61% yield. IR (KBr): ν_{max} 3265 (NH), 2925, 2855 (CH_2), 1699 (CO) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 0.85(t, 3H, CH_3-), 1.28–1.7 (m, 16N, 8 × CH_2-), 1.73–1.96 (m, 2H, CH_2-), 1.96–2.16 (m, 4H, 2 × CH_2-), 2.18–3.03(m, 6H, 3 × CH_2-), 4.07–4.17 (d, 1H, *J* = 14.31 Hz, CH-), 4.34–4.40 (dd, 1H, *J* = 2.31 and 11.87 Hz, CH-), 5.31(m, 2H, CH=CH), 7.55 (m, 10H, 2 × Ph), 8.23(brs, 1H, NH) ppm. MS: *m/z*(%) = 612 [M^+]. Anal. Calcd for $C_{38}H_{47}ClN_4O$ (611.26): C, 74.67; H, 7.75; N, 9.17. Found: C, 74.80; H, 7.60; N, 9.20%.

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